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Role of circulating lipid abnormalities in chronic renal allograft rejection

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Role of circulating lipid abnormalities in chronic renal allograft rejection. The evidence that circulating lipid abnormalities may play a role in the pathogenesis of chronic renal allograft rejection is tantalizing but circumstantial. In animal models of cardiac and aorta allograft rejection, lipogenic diets accelerate vascular injury, and treatment with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors reduce vascular injury. Histological studies have demonstrated foam cells and apolipoprotein deposits in the intima of arteries from chronically rejecting human kidneys. Observational studies have found correlations between plasma lipid levels and both acute and chronic rejection. The association between lipid levels and acute rejection in cyclosporine A (CsA)-treated renal transplant recipients suggests the possibility that plasma lipids may influence the immunosuppressive effects of CsA by modulating the lipoprotein-free levels of CsA. If true, such an effect could also explain the results of recent controlled trials showing that HMG-CoA reductase inhibitors reduced graft coronary artery disease and that they prolonged survival in heart transplant recipients. In any case, the hypothesis that circulating lipid abnormalities contribute to chronic renal allograft rejection deserves further testing in well-designed, clinical trials.

Based on the results of both experimental animal investigations and clinical observational studies, it has been hypothesized that chronic rejection may be caused by both immune and nonimmune factors. That circulating lipoprotein abnormalities may contribute to chronic renal allograft rejection is suggested by several observations: (*a*) Experiments using animal models of chronic rejection have suggested that lipid abnormalities may contribute to allograft vasculopathy. (*b*) The most distinctive histological finding in chronic rejection is a form of allograft vasculopathy that resembles, in many ways, systemic atherosclerosis. (*c*) The same circulating lipid abnormalities that have been implicated in the pathogenesis of systemic atherosclerosis are common in renal transplant recipients, and circulating lipid abnormalities appear to be more common in patients with chronic rejection. (*d*) The vasculopathy that characterizes chronic renal allograft rejection is similar to that seen in heart transplant recipients, and randomized, controlled trials have reported that 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase inhibitors reduce cardiac allograft vasculopathy and prolong survival [1, 2].

Although there are cogent reasons to believe that circulating lipid abnormalities may contribute to chronic rejection, the data arguing in favor of this hypothesis are largely circumstantial. Confounding the interpretation of observational data and controlled trials is the possibility that lipid levels may indirectly influence chronic rejection by altering levels of free cyclosporine A (CsA), that is, CsA that is not bound to lipoproteins. Higher levels of free CsA may lead to greater immunosuppression and may thereby explain at least some of the relationship between lipid levels and renal allograft rejection.

EVIDENCE FROM ANIMAL MODELS

Lipogenic diets accelerate coronary artery disease of rat and rabbit cardiac allografts in the absence of immunosuppression [3, 4]. More recently Tanaka, Sukhova, and Libby reported that a lipogenic diet also worsened coronary lesions in a rabbit cardiac transplant model immunosuppressed with CsA [5]. Similarly, a lipogenic diet accelerated vascular injury in a rat aorta allograft model [6]. Treatment with the HMG-CoA reductase inhibitors has been shown to reduce cardiac allograft vasculopathy in rats [7]. Although oxidized lipoproteins are felt to be important in the pathogenesis of systemic atherosclerosis, the antioxidant Probucol failed to improve vascular injury in rabbit aorta allografts when cholesterol levels were kept constant with diet [8].

HISTOLOGICAL EVIDENCE

The first report of successful cadaveric renal transplantation in humans included a description of allograft vasculopathy characteristic of chronic rejection [9]. There are many similarities and differences between the

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vascular lesions seen in chronic rejection and those that characterize systemic atherosclerosis. The vascular lesions seen in chronic renal allograft rejection are made up of macrophages, foam cells, lymphocytes, and proliferating smooth muscle cells. In addition, vascular lesions from chronically rejecting renal allografts contain apolipoprotein deposits, specifically apolipoproteins A-I, A-II, and B [10]. However, it is possible that arterial lipoprotein deposition is a passive phenomenon and is the result rather than the cause of vascular injury.

Because oxidized lipoproteins may play an important role in the pathogenesis of systemic atherosclerosis, Tanabe et al looked for evidence of oxidized lipoproteins in arteries from 10 rejecting renal allografts [11]. Using a monoclonal antibody to oxidized low-density lipoprotein (LDL), they found that four of the five individuals who had hypercholesterolemia (>240 mg/dl) had evidence for oxidized LDL in the vascular intima. In contrast, none of the five patients with cholesterol of less than 240 mg/dl had evidence for oxidized LDL in allograft arteries [11]. Thus, it is possible that oxidized lipoproteins could play a role in the pathogenesis of chronic allograft vasculopathy in hypercholesterolemic patients.

EVIDENCE FROM OBSERVATIONAL STUDIES

Several investigators have found that transplant recipients with hyperlipidemia are more likely to have chronic rejection. Isoniemi et al examined risk factors among 98 consecutive renal allograft recipients who survived with a functioning allograft for at least two years [12]. They found that levels of total cholesterol, LDL cholesterol, and triglycerides correlated with subsequent chronic declines in allograft function. However, proteinuria was not measured in this study, and it is possible that patients destined to have declines in function already had graft injury that caused the elevated lipid levels. It is interesting, therefore, that Dimény et al found that pretransplant cholesterol levels predicted late graft failure [13]. It was noteworthy that pretransplant cholesterol levels also correlated with acute rejection episodes during the first six months after transplantation [14], and acute rejection is a strong risk factor for late graft failure. Because most of these patients were treated with CsA, it is interesting to speculate whether serum lipid levels influenced the biological effects of CsA. Because CsA binds to lipoproteins, patients with lower plasma lipid levels might have higher free CsA drug levels. If the free fraction is important for cell uptake, then plasma lipid levels could influence the immunosuppressive and toxic effects of CsA. Indeed, CsA toxicity may be more common in patients with low plasma lipid levels [15].

We examined the relationship between post-transplant lipid levels and graft loss to chronic rejection in a cohort of patients who survived at least six months with a functioning allograft [16]. Only 250 of the 706 patients in this cohort ever received CsA, and most of these patients had the CsA electively withdrawn one year after transplantation [17]. Using time-dependent covariates in a multivariate Cox proportional hazards analysis, we found that serum triglycerides, but not cholesterol, were independent risk factors for graft loss to chronic rejection [16]. It is interesting to speculate whether the lack of effect of serum cholesterol, in contrast to the findings of others [12, 13], could be due to the fact that few of our patients received long-term CsA therapy.

There is also evidence for an increased prevalence of oxidized lipoproteins after renal transplantation. Ghanem et al found that LDL particles were smaller in renal transplant recipients compared with controls, suggesting a greater tendency for LDL to become oxidized [18]. This was confirmed by showing that the lag time for copper oxidation of LDL was reduced in transplant recipients [18]. In addition, monoclonal antibodies to oxidized LDL were higher in transplant recipients compared with controls [18]. All of this provides strong circumstantial evidence that oxidized LDL is more common in renal transplant recipients than in normal individuals. Similarly, Cristol et al found that renal transplant recipients with histologically confirmed chronic rejection had increased plasma levels of malondialdehyde, an end product of lipid peroxidation [19].

INTERVENTION TRIALS

Two randomized, controlled clinical trials have demonstrated that HMG-CoA reductase inhibitors reduced the severity of angiographic coronary artery disease and improved patient survival following cardiac transplantation [1, 2]. If the pathogenesis of allograft vasculopathy in renal and cardiac transplant recipients is similar, then HMG-CoA reductase inhibitors may hold promise for preventing and/or treating chronic renal allograft rejection as well. However, the mechanism whereby HMG-CoA reductase inhibitors improved survival in heart transplant recipients is still not entirely clear. It is possible that the HMG-CoA reductase inhibitors had a direct, immunosuppressive effect. If so, then the effect must require the presence of CsA, as suggested by the investigators, because there is no evidence that HMG-CoA reductase inhibitors are immunosuppressive in normal individuals. However, an alternative explanation is that the reduction in lipids caused by the HMG-CoA reductase inhibitors increased the immunosuppressive effect of CsA in the manner described earlier here. Clearly, additional studies will be needed to understand better the mechanisms behind the improved patient and graft survival seen with HMG-CoA reductase inhibitors. In the meantime, it is likely that the best therapeutic approach for chronic rejection may ultimately be a combi-

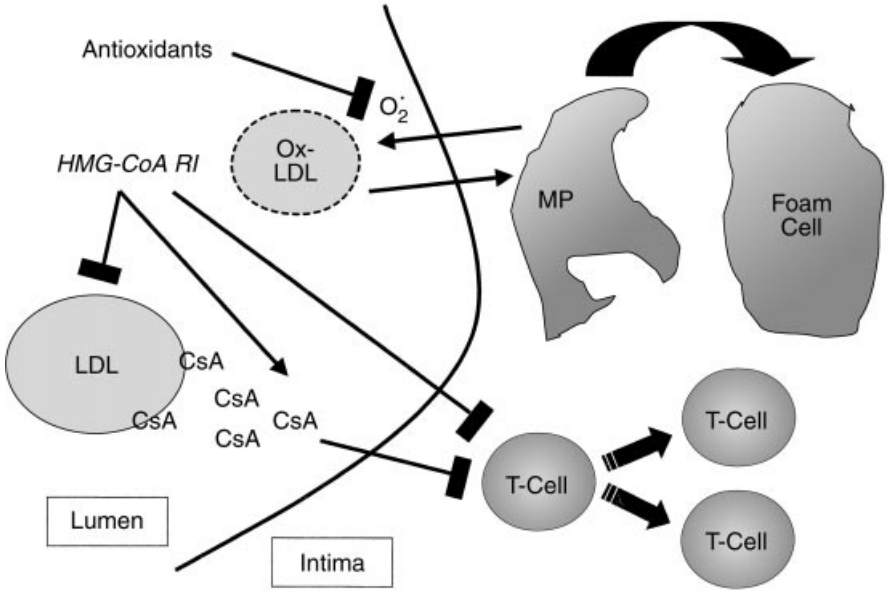

Fig. 1. Potential role of antilipemic therapy in chronic allograft rejection. 3-Hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase inhibitors may decrease low density lipoprotein cholesterol levels, which, in turn, could theoretically increase free cyclosporine A (CsA) levels. CsA could reduce intimal damage by inhibiting T lymphocytes. Antioxidants could reduce the formation of oxidized low-density lipoprotein and thereby reduce foam cell formation. Abbreviations are: LDL, low-density lipoprotein; MP, macrophage.

nation of antilipemic, immunosuppressive, and possibly antioxidant agents (Fig. 1).

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